REMARKS

Claims 1-46 were pending. Applicants note that the Office Action Summary incorrectly stated that only claims 1-4, 11-14, and 28-43 were pending. Claims 5-10, 15-20, 22-27, 30, 31, 33, 34, 37, and 38 are also pending and have been withdrawn as drawn to non-elected inventions or species.

Claim 21 has been cancelled without prejudice. Applicants reserve the right to prosecute the subject matter of the canceled claim in one or more related applications. Claims 1 and 11 have been amended to clarify that which Applicants believe to be the invention. In particular, the recitation of peptide linkers having the amino acid sequence Phe Arg Lys; Phe Arg Lys Asn; Arg Lys Asn; Phe Phe Arg Lys Asn; Phe Arg; Gln Leu Lys; Gln Leu Glu; Ala Lys Val Leu; Lys Asn; Arg Lys; or AA_1-AA_2-AA_3-leucine, wherein AA_1 is Ala, Ser, Val, Glu, Gly, Leu, or Lys, AA_2 is Lys, Val, or Glu, and AA_3 is Val, Ser, Phe, Lys, Ala, Glu, or Thr has been deleted from claims 1 and 11. Accordingly, no new matter is introduced. Upon entry of the amendments made herein, claims 1-20 and 22-46 will be pending.

The drawing description in the substitute specification filed on January 21, 2005 has been amended to indicate which sequence identifier (SEQ ID NO) pertains to each amino acid sequence depicted in Figure 1. In particular, paragraph [0036] at page 16 of the substitute specification has been amended to include SEQ ID NO:868 for the amino acid sequence SIINFEKL and SEQ ID NO:881 for the amino acid sequence NLLRLTGWFFRKSIINFEKL. Support for this amendment can be found in the specification, as filed, in Figure 1 and at page 68, lines 4-13. In addition, the substitute specification has been amended to correct the inadvertent spelling error in the word "described." As such, no new matter is introduced.

Election/Restriction

Applicants hereby confirm the provisional election with traverse of the species herpes virus as an infectious agent with respect to the claims of elected Group I.

Objection to the Specification

The Examiner objects to the specification for failing to indicate which sequence identifier pertains to each amino acid sequence depicted in Figure 1. In response, Applicants point out that the specification was amended on January 21, 2005 to insert the appropriate

sequence identifiers for the sequences. Nevertheless, Applicants have amended the specification in paragraph 36 to indicate the sequence identifiers for the amino acid sequences SIINFEKL (SEQ ID NO:868) and NLLRLTGWFFRKSIINFEKL (SEQ ID NO:881), which are depicted in Figure 1. Thus, Applicants respectfully request that the objection to the specification be withdrawn.

The Rejection Under 35 U.S.C. § 103(a) Should be Withdrawn

The Examiner has rejected claims 1-4, 11-14, 28, 29, 32, 35, 36, and 39-43 under 35 U.S.C. § 103(a) as being unpatentable over Wieland et al., U.S. Patent Application Publication No. 2004/0071656 ("Wieland"). The Examiner contends that Wieland teaches (i) a composition of a heat shock protein non-covalently linked to an antigen via a polypeptide (at least 5 amino acids long) that can be used in inducing an immune response in a mammal; and (ii) infectious disease antigens such as herpes virus that can be non-covalently linked to a heat shock protein such as hsc70, which can also function as an adjuvant. Further, the Examiner states that the different sizes and compositions among those polypeptides in Wieland would motivate one in the art to use multiple polypeptide sequences in developing a hybrid antigen bound to hsc70.

In response, Applicants submit that claims 1-4, 11-14, 28, 29, 32, 35, 36, and 39-43 are not obvious in view of Wieland for the reasons set forth below.

The Legal Standard

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim: (1) the cited references, when combined, teach or suggest every element of the claim; (2) there is some suggestion or motivation to modify the reference or combine the reference teachings to arrive at the claimed invention; and (3) there must have been a reasonable expectation of success for making the claimed combination in the art at the time of filing. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not in the applicant's disclosure. *Id.*

Also, evidence of unexpected or unobvious results is objective evidence of nonobviousness, and may be used to rebut a *prima facie* case of obviousness. *In re Wagner*, 371 F.2d 877 (C.C.P.A. 1967); M.P.E.P. § 716.02. A declaration demonstrating the

unexpected result that the claimed compound possesses superior activity relative to the prior art is sufficient to rebut a *prima facie* case of obviousness. *In re Chupp*, 816 F.2d 643, 646 (Fed. Cir. 1987); *Ex parte A*, 17 U.S.P.Q.2d 1716, 1718 (Bd. Pat. App. & Inter. 1990).

The Claimed Invention of the Instant Application Provides Unexpected Results.

Claim 1 is directed to a hybrid antigen comprising at least one antigenic domain of an infectious agent (*i.e.*, an antigenic domain of herpes virus) or tumor antigen, at least one binding domain that non-covalently binds to a heat shock protein, and at least one peptide linker there between consisting of the amino acid sequence Phe Phe Arg Lys ("FFRK peptide linker").

Wieland discloses that a heat shock protein can be non-covalently bound to a hybrid antigen, which comprises an antigenic domain, a heat shock protein binding domain (Wieland at ¶128), and optionally a short peptide linker that may be interposed between the antigenic domain and heat shock protein binding domain (Wieland at ¶¶ 13 and 20). In particular, the short peptide linker can be the Gly-Ser-Gly ("GSG") peptide linker (see Wieland at ¶158). Wieland further discloses a list of amino acid sequences as non-limiting examples of heat shock protein binding domain peptides (Wieland at ¶¶ 129-131) and a list of antigens, including herpes virus antigens, for conjugation to a heat shock protein binding peptide (Wieland ¶147). Wieland does not teach or suggest the improved peptide linker of the claimed invention that is covalently joined between the antigenic domain and the heat shock protein binding domain and that consists of the amino acid sequence Phe Phe Arg Lys.

Moreover, Applicants submit that the claimed invention exhibits surprising results, in that the presence of the FFRK peptide linker between the antigenic domain and the heat shock protein binding domain in a hybrid antigen leads to an increase in biological activity, *i.e.*, an increase in induced immune response against the antigenic portion of the hybrid antigen (specification at ¶9), relative to a comparable hybrid antigen comprising the GSG peptide linker.

In support of the foregoing, the Examiner's attention is directed to the Declaration of Dr. Jessica B. Flechtner Under 37 C.F.R. § 1.132 ("the Flechtner Declaration") submitted herewith. The Flechtner Declaration discusses the evidence indicating the unexpected result achievable with the use of the claimed hybrid antigen of the present invention. Dr. Flechtner states that "[t]he unexpected result is that immunization with a hybrid antigen comprising the FFRK peptide linker, the hybrid antigen being alone or noncovalently complexed to a heat shock protein, is more effective at inducing an immune response against the antigenic domain

of the hybrid antigen than immunization with a comparable hybrid antigen comprising the GSG peptide linker instead of the FFRK peptide linker, noncovalently complexed to a heat shock protein" (the Flechtner Declaration at ¶9).

The Flechtner Declaration discusses the evidence in Example 4 of the specification of the present application that demonstrates the unexpected result achievable with the use of the claimed hybrid antigen of the present invention:

> In the interferon-γ (IFN-γ) ELISPOT assay of Example 4, the immunogenic activity of hybrid antigens containing either the FFRK peptide linker ("the FFRK hybrid antigen") or the GSG peptide linker ("the GSG hybrid antigen") were compared. Both hybrid antigens contained the same heat shock protein binding domain having the amino acid sequence NLLRLTGW and antigenic domain having the amino acid sequence SIINFEKL, a MHC Class I ovalbumin epitope. Mice were immunized subcutaneously at the base of the tail with Hsp70 alone, Hsp70 noncovalently complexed with the SIINFEKL epitope, or Hsp70 noncovalently complexed with the FFRK hybrid antigen or the GSG hybrid antigen. Seven days after immunization, $CD8^+$ T cells were purified from the harvested spleens of the immunized mice and were assayed in an IFN-γ ELISPOT assay to measure IFN-γ secretion by $CD8^+$ T cells upon exposure to the SIINFEKL epitope (see the '067 application at pages 60-61). IFN-γ secretion by $CD8^+$ T cells upon recognition of the target antigen is an indication of $CD8^+$ T cell activation and specific $CD8^+$ T cell response against the target antigen. Results of the IFN-γ ELISPOT assay are reported in the table in Example 4 as the average number of spots per 400,000 $CD8^+$ T cells from at least 4 experiments (the '067 application at pages 60-61). Controls included medium alone, unpulsed T cells, T cells pulsed with a non-immunized peptide derived from VSV (negative control), or T cells pulsed with Concanavalin A (positive control) (see the '067 application at pages 60-61). As shown in the table in Example 4, approximately three times more spots were detected in samples with $CD8^+$ T cells from mice immunized with the FFRK hybrid antigen noncovalently complexed to Hsp70 than in samples with $CD8^+$ T cells from mice immunized with the GSG hybrid antigen noncovalently complexed to Hsp70, when the $CD8^+$ T cells were pulsed with the SIINFEKL epitope. The ^{51}Cr-release assay result in Example 4 is consistent with the IFN-γ ELISPOT result. Target cells were intracellularly labeled with the ^{51}Cr radioisotope, pulsed with the SIINFEKL epitope, and cultured with $CD8^+$ T cells purified from the same immunized mice used in the ELISPOT assay described above. Target cells that are recognized and killed by $CD8^+$ T cells release ^{51}Cr into the media, and the amount of ^{51}Cr released into the media was used to calculate the percentage of target cell killing at a ratio of 200 effector $CD8^+$ T cells per one target cell. As shown in the right column of the table in Example 4,

> $CD8^+$ T cells isolated from mice immunized with the FFRK hybrid antigen noncovalently complexed to Hsp70 achieved a higher percentage of target cell killing than $CD8^+$ T cells isolated from mice immunized with the GSG hybrid antigen noncovalently complexed to Hsp70.

(the Flechtner Declaration at ¶10).

The Flechtner Declaration also discusses the evidence in Examples 5 and 6 of the specification of the present application that demonstrates the unexpected result achievable with the use of the claimed hybrid antigen of the present invention:

> As shown in the tables in Examples 5 and 6, $CD8^+$ T cells from mice immunized with the FFRK hybrid antigen, alone or noncovalently complexed to Hsp70, produced a higher response that is specific to the SIINFEKL epitope of the antigenic domain than $CD8^+$ T cells from mice immunized with the GSG hybrid antigen noncovalently complexed to Hsp70. In Example 5, immunization with the FFRK hybrid antigen alone or noncovalently complexed to Hsp70 resulted in approximately a 12-fold and 64-fold increase, respectively, in $CD8^+$ T cell response to the SIINFEKL epitope relative to immunization with the GSG hybrid antigen noncovalently complexed to Hsp70 (the '067 application at page 62). In Example 6, immunization with the FFRK hybrid antigen alone or noncovalently complexed to Hsp70 resulted in approximately a 1.6-fold and 5-fold increase, respectively, in $CD8^+$ T cell response to the SIINFEKL epitope relative to immunization with the GSG hybrid antigen noncovalently complexed to Hsp70 (the '067 application at page 63).

(the Flechtner Declaration at ¶11).

Dr. Flechtner states that the evidence provided in Examples 4-6 of the specification of the present application "clearly shows that immunization with a hybrid antigen comprising the improved FFRK peptide linker of the '067 application [the present application], alone or noncovalently complexed to a heat shock protein, is unexpectedly more effective at inducing an immune response to the antigenic domain epitope of the hybrid antigen relative to immunization with a hybrid antigen comprising the conventional GSG peptide linker and noncovalently complexed to a heat shock protein" (the Flechtner Declaration at ¶12). Also, Dr. Flechtner opines that "an ordinarily skilled researcher in the field would not have expected that substituting the GSG peptide linker with the FFRK peptide linker would significantly affect the immunogenic activity of the hybrid antigen when used alone or in a noncovalent complex with a heat shock protein" (the Flechtner Declaration at ¶9).

In view of the unexpected results described in the Flechtner Declaration and in the specification of the present application, Applicants submit that the claimed hybrid antigen of the present application is not obvious in view of Wieland. The results achievable with use of the claimed hybrid antigens of the instant application are unexpectedly superior to the results achieved with the use of hybrid antigens known in the art, *i.e.*, hybrid antigens comprising an antigenic domain, a heat shock protein binding domain, and the GSG peptide linker there between. Further, Wieland does not teach or suggest the FFRK peptide linker, and thus the claimed hybrid antigen containing the FFRK peptide linker, of the invention. Nor is there any suggestion or expectation in the art that substituting the prior art GSG peptide linker with the FFRK peptide linker would result in an improved hybrid antigen with the ability to elicit an increased immune response against the antigenic portion of the hybrid antigen.

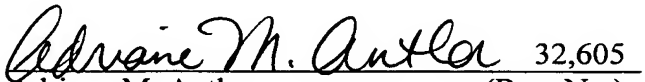
Thus, Applicants respectfully request that the rejection of claims 1-4, 11-14, 28, 29, 32, 35, 36, and 39-43 under 35 U.S.C. § 103(a) as being obvious over Wieland be withdrawn.

CONCLUSION

Applicants respectfully request that the above remarks and amendments be entered and made of record in the file history of the instant application.

Respectfully submitted,

Date: March 20, 2007



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